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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/942,310	08/29/2001	Carl Risinger	524592001900	7722

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

* Supplemental * Office Action Summary	Application No. 09/942,310	Applicant(s) RISINGER ET AL.	
	Examiner Jeanine A. Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-32* is/are pending in the application.

4a) Of the above claim(s) *20-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19 and 27-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Finality of the Office Action Mailed March 23, 2005 has been withdrawn.

2. This action is in response to the papers filed December 8, 2004. Currently, claims 17-32 are pending. Claims 20-26 have been withdrawn as drawn to non-elected subject matter.

3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

4. Any objections and rejections not reiterated below are hereby withdrawn.

5. This action contains new grounds of rejection necessitated by amendment.

Election/Restrictions

6. Claims 20-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Priority

7. This application claims priority to UK 0021286.0, filed August 30, 2000.

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

8. The drawings are acceptable.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 17, 27-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for predicting a human's capacity to metabolize a substrate of a CYP2D6 enzyme by identifying polymorphic sites in a CYP2D6 flanking region.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written

description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

With respect to claims which encompass three or more polymorphic variants. As provided in Example 11, no common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the four polymorphisms taught in the CYP2D6 flanking region alone is insufficient to describe the genus. The CYP2D6 upstream flanking region is over 1620 nucleotides in length. The specification does not particularly distinguish what is encompassed by the CYP2D6 flanking region. Further, there is no description of the mutational sites that exist in nature and there is no description of how the structure of polymorphisms in the CPY2D6 flanking region relates to the structure of any strictly neutral alleles. The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one

does not provide guidance to the structure of others. The common attributes are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 17-19, 27-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining a Sweedish Caucasian human's capacity to metabolize desbrisoquine, a substrate of the CYP2D6 enzyme, by identifying the three polymorphic sites at positions –590, -1338, -1496, but does **not** reasonably provide enablement for;

- Detecting any race of human's capacity to metabolize a substrate of CYP2D6through the identification of three or more polymorphic sites in the CYP2D6 gene.
- Detecting the above capacity to metabolize any substrate of CYP2D6, besides desbrisoquine.
- Detecting any three or more polymorphic sites in any CYP2D6 flanking region.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 17-19, 27-32 are broadly drawn to a method of determining a human of any race's capacity to metabolize any substrate of CYP2D6 through the identification of any three or more polymorphic sites in any flanking region of CYP2D6. The claims are so broad as to encompass the method's execution with; any SNP located in a "CYP2D6 flanking region", any race of human having these broadly recited SNPs, and detecting the above capacity to metabolize any substrate of CYP2D6. However, as will be further discussed, there is no support in the specification and prior art for the methods as broadly as they are currently claimed. The invention is in a class of invention that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The specification recites that "for these experiments, a single dose of 10 mg debrisoquine was taken in the evening before bed"(lines 10-12 pg. 17), and furthermore that "in the first part of the study, 88 samples(Swedish Caucasians) were selected as set forth in Table 1"(Spec pg. 13). In table 11, the specification teaches the statistically relevant p-values of haplotypes H1-H4 as defined in Table 10 also on page 25 of the specification. In table 13 on page 26, the specification teaches the CYP2D6 genotypes and haplotypes that are associated with a particular capacity to metabolize debrisoquine, the only taught substrate of CYP2D6 (i.e. Ultra Extensive Metabolizers(UEM), Extensive metabolizers(EM), Intermediate metabolizers(IM), or Poor metabolizers(PM) along with the observed metabolic ratios of debrisoquine. However, there is no teaching of any other SNP in the flanking region of CYPD6, besides those enumerated in Table 10, that are associated with an observed capacity to metabolize debrisoquine. Furthermore, only a single population of Swedish Caucasians is taught to be a part of the specification's findings. Lastly, only debrisoquine is taught as a substrate of CYP2D6 to yield these metabolic capacities. The specification omits any teachings of results obtained with a diverse population of all races, testing for metabolic capacities achieved by treatment with a diverse group of substrates of CYP2D6 other than debrisoquine, and any SNP located in the flanking region of CYP2D6.

First, regarding the unpredictability associated with claiming any SNP located in the flanking region of CYP2D6, there exists a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic

sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated. As a result, there is a great deal of unpredictability that exists in the invention without any guidance in the specification for example, to any polymorphism located in the flanking region of CYP2D6 gene other than those enumerated in Table 10 of the specification, being correlated to any metabolic capacity. With respect to the unpredictability involved with a method related to the cytochrome

genes being applicable to a human of any race, additional prior art corroborates the unpredictability in Goldstein et al's teaching that "the frequency of this polymorphism[that of CYP2C19] varies markedly in different racial populations, with the PM phenotype representing 2-5% in Caucasian populations, but from 13-23% in Oriental populations"(Pharmacogenetics, 1997, 7; page 59 bottom right). Goldstein et al. further teach that "the present results indicate complete concordance between phenotype and genotype in three Oriental racial groups, while the incidence of the CYPD6m1 allele is higher in Oriental races than in Caucasians or African-Americans...Saudi Arabians were found to resemble Caucasians in both the incidence of CYPD6m1 and relative absence of CYPD6m2"(Goldstein et al, Pg 63 bottom left side). Concerning the substrate being claimed, applicant provides no teaching of a general quality had by every substrate that their claim presently reads on. As a result, the presently filed specification provides enablement for only that of debrisoquine.

The post filing date art further supports the unpredictability involved in extrapolating the results of a study with one distinct Caucasian population to all races as Ozawa et al. teach "that it is a matter of primer importance to take interracial differences into account in the frequency of genetic polymorphisms of drug-responsive genes"(Introduction, Drug Metab. Pharmacokin. 19(2); 83-95(2004). The reference continues by teaching that ethnic differences of CYP2D6 in "Chinese, African, Swedish, and Spanish are schematically outlined in Fig. 1...that clearly indicated the existence of a considerable number of poor metabolizers showing high metabolic ratios in European Caucasians (Swedish and Spanish) at a frequency of approximately 7% but PMs are relatively rare in the Chinese(1%)"(Page 84 left side). Table 1 illustrates ethnic differences in vivo metabolic capacity for CYP2D6 substrates. Ozawa teaches

desipramine and codeine as substrates. There is a significant difference between codeine in Caucaisans and Chinese (page 84).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there are a significant number of parameters which would have to be studied to apply this method to the broadly claimed embodiments involving any SNP in the flanking region of CYP2D6, in any race, and with any substrate to CYP2D6. The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention as asserted by the specification, one would have to establish a relationship between non-existent SNPs in the undefined region flanking CYP2D6 with some capacity to metabolize debrisoquine, or some other substrate of CYP2D6. In order to obtain the type of information necessary to practice the claimed invention, one would be required to undertake the screening of hundreds or thousands of patients of all races as well as possible hundreds of pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would still be detected considering the new diversity of experimental variables, and further in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method is useful as broadly as it is claimed, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between the polymorphism in any race and to any capacity for metabolism.

Raimundo et al. (Pharmacogenetics, Vol. 10, pages 577-581, October 2000) teaches analyzing haplotypes for their ability to metabolize. Table 1 illustrates

individuals and their genotypes and the metabolic rations. In table 1, an individual with CTG (nucleotides –1496; -1338; -590) would be considered both a poor metabolizer and an intermediate metabolizer. The MR for these two haplotypes would be 205 and 2.1. The difference between these two values which both appear to have the same three polymorphisms is significant. The mutation at –1447 appears to be the difference which causes MR to differ. Further, the instant specification teaches the H4 is a poor metabolizer whereas Raimundo teaches H4 is either poor or intermediate metabolizer. It is noted that the instant claims do not specifically set forth which nucleotides are associated with a particular haplotype and further which ranges of metabolizers are indicative of different capacities.

This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Working Examples

The specification has no working examples of the method using any SNP in the region flanking the CYP2D6 gene, using any population other than a Swedish Caucasian one, to detect a capacity for metabolizing any substrate other than debrisoquine.

Guidance in the Specification.

The specification provides no evidence that the disclosed method would be effective if practiced as broadly as it is claimed. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely

discloses that "for these experiments, a single dose of 10 mg debrisoquine"(lines 10-12 pg. 13), and furthermore that "in the first part of the study, 88 samples(Swedish Caucasians) were selected as set forth in Table 1"(Spec pg. 13). In table 11, the specification teaches the statistically relevant p-values of haplotypes H1-H4 as defined in Table 10 of the specification. In table 13, the specification teaches the CYPD6 genotypes and haplotypes that are associated with a particular capacity to metabolize debrisoquine, the only taught substrate of CYPD6(i.e. Ultra Extensive Metabolizers(UEM), Extensive metabolizers(EM), Intermediate metabolizers(IM), or Poor metabolizers(PM) along with the observed metabolic ratios of debrisoquine. Even if, arguendo, the detected SNPs in the flanking region of CYPD6 are correlated with some capacity of metabolism, there is no support for the same, prophetic correlation in any race being studied.

Table 13 is specifically drawn to haplotype pairs. The specification teaches that a haplotype pair with H4 may be a poor metabolizer (H4/H4) and also extensive metabolizer, (H2/H4). Thus, based upon the teachings in the specification, the skilled artisan, without knowing the full genetic make up of the individual for haplotype pairs (both copies of an individual's genome), a correlation to the human's capacity to metabolize a substrate would be unpredictable. The mere detection of H4 would not provide the skilled artisan with enough information to predictably indicate the capacity to metabolize a substrate.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the use of SNPs to detect disease states is even further unpredictable, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Conclusion

11. No claims allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Jeanine Goldberg
Primary Examiner
August 19, 2005